IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: Schnellmann et al	§	ART UNIT: 1614
FILED: July 5, 2001	§	
SERIAL NO.: 09/899,704	§	EXAMINER: Cook, R.
FOR: Use of Ascorbic Acid and Salts of Ascorbic Acid to Promote Cell Repair and Regeneration after Injury	§	DOCKET: D6305

Mail Stop Appeal Brief - Patents
Commissioner of Patents
P.O. Box 1450
Alexandria, VA 22313

ATTENTION: Board of Patent Appeals and Interferences

APPELLANT'S BRIEF

This Brief is in furtherance of the Notice of Appeal filed in this case on May 8, 2003. The fees required under 37 C.F.R. §1.17(f) and any other required fees are dealt with in the accompanying TRANSMITTAL OF APPEAL BRIEF.

In accordance with 37 C.F.R. §1.192(a), this Brief is submitted in triplicate.

INDEX OF SUBJECT MATTER

I. REAL PARTY IN INTEREST

The real party in interest is University of Arkansas For Medical Sciences, the Assignee, as evidenced by an Assignment recorded in the Patent and Trademark Office at Reel 012731, Frame 0825 on March 19, 2002.

II. RELATED APPEALS AND INTERFERENCES

Appellant is aware of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF THE CLAIMS

Originally claims 1-17 were filed with this Application. Claims 2, 5-10, 14 and 17 were canceled by amendment. The pending claims 1, 3-4, 11-13, 15-16 are being appealed of which claims 1, 11 and 15 are independent claims.

IV. STATUS OF AMENDMENTS

Subsequent to the Final Office Action mailed November 5, 2002, Applicant submitted a Response After Final which canceled claims 5-10 and 17 and amended claims 1, 11, 15-16. In the Advisory Action mailed April 23, 2003, the Examiner indicated that the proposed amendments will be entered upon appeal. All pending claims are shown in Appendix A.

V. SUMMARY OF THE INVENTION

The present invention was designed to test whether pharmacological concentrations of L-ascorbic acid phosphate can promote cellular recovery after injury induced by halocarbon nephrotoxicant such as dichlorovinyl-L-cysteine (page 35, lines 16-20; page 7, lines 2-5). It was demonstrated that ascorbic acid is a strong promoter of cell repair and regeneration, promoting cellular proliferation (page 27, line 14 to page 28, line 3), mitochondrial function (page 28, line 20 to page 29, line 4; page 29, line 17 to

page 30, line 1), Na^+-K^+-ATPase protein expression (page 32, line 13 to page 33, line 4), Na^+-K^+-ATPase protein activity and active Na^+ transport (page 30, lines 7-10; page 31, lines 3-5). The mechanism by which ascorbic acid produces this effect is not through its known antioxidant properties (see Abstract; page 7, line 7 to page 8, line 1). These results indicate that the beneficial effects of pharmacological concentrations of ascorbic acid are not limited to antioxidant action of this molecule and that ascorbic acid may be an important tool in promoting cellular recovery following toxicant-induced injury (page 8, lines 1-5).

VI. ISSUES

35 U.S.C. §103

Whether claims 1, 3-4, 11-13 and 15-16 are unpatentable over U.S. Pat. No. 4,711,780 (**Fahim**), U.S. Pat. No. 5,230,996 (**Rath**), **Saika** (abstract, 1993) or **Nowak** (abstract, 1997) alone or in combination under 35 U.S.C. §103(a).

VII. GROUPING OF CLAIMS

The rejected claims do stand or fall together.

VIII. ARGUMENTS

Rejection Under 35 U.S.C. §103

Claims 1, 3-4, 11-13, and 15-16 were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Pat. No. 4,711,780 (**Fahim**), U.S. Pat. No. 5,230,996 (**Rath**), **Saika** (abstract, 1993) or **Nowak** (abstract, 1997) alone or in combination. Applicants respectfully request that this rejection be reversed.

The present invention demonstrates that pharmacological concentrations of L-ascorbic acid phosphate (vitamin C) can promote cellular recovery after injury induced by a model halocarbon toxicant dichlorovinyl-L-cysteine. L-ascorbic acid phosphate promotes recovery of cellular proliferation, mitochondrial function, Na^+-K^+-ATPase protein expression, Na^+-K^+-ATPase protein activity, and active Na^+ transport. It is important to

note that the present invention teaches L-ascorbic acid phosphate acting alone is capable of promoting cellular recovery after injury caused by halocarbon toxicant.

In contrast, **Fahim** teaches a medication for the treatment of epithelial tissue comprising vitamin C, a zinc salt and a sulfur amino acid. **Rath** teaches a solution of ascorbate and tranexamic acid for the treatment or prevention of cardiovascular disease. **Fahim** and **Rath** only teach combinations of vitamin C and other compounds. **Fahim** and **Rath** do not teach or suggest vitamin C would be effective or useful when used alone as claimed herein. Hence, **Fahim** and **Rath** actually teach away from the instant invention.

Saika teaches the effect of ascorbic acid or ascorbic acid phosphate on alkali burns in the corneas of rabbits. The effects observed include an increase in non-burned stroma and basal lamina under new epithelia.

Nowak teaches ascorbic acid stimulates cellular regeneration in cells exposed to a model oxidant tert-butylhydroperoxide (TBHP). Ascorbic acid promoted regeneration

by stimulating proliferation and cell migration/spreading and decreasing cell death during the recovery period.

The Examiner contends that each of the cited prior art discloses that ascorbic acid phosphate and ascorbic acid promote recovery of cellular functions following injury caused by a variety of conditions, including toxic substances (Office Action mailed March 20, 2002, page 4). The Examiner concludes that the claims of the present invention differ from the cited prior art in reciting a specific toxic substance. According to the Examiner, once a method of using a compound is known to treat injury, no unobviousness is seen in an injury caused by a specific toxic substance (Office Action mailed March 20, 2002, page 4). Applicant respectfully disagrees.

Applicants respectfully submit that the Examiner has not provided clear evidentiary proof that demonstrates the required suggestion or motivation to modify the cited references to arrive at the instant invention. In contrast, the Examiner has only provided broad conclusory remarks without giving a reasoned argument based on the Graham factual inquiries.

To establish a *prima facie* case of obviousness, three

basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (M.P.E.P. §2143). Applicant submits that the Examiner has not met these three basic criteria.

First of all, there is no suggestion or motivation to modify any of the cited references to use L-ascorbic acid phosphate alone to recover mitochondrial function, Na^+-K^+-ATPase protein expression, Na^+-K^+-ATPase protein activity, and active Na^+ transport as claimed herein.

As discussed above, **Fahim** and **Rath** do not teach or suggest ascorbic acid phosphate would be effective or useful when used alone as claimed herein. Neither did **Fahim** and **Rath** teach or suggest recovery of mitochondrial function, Na^+-K^+-ATPase protein expression, Na^+-K^+-ATPase protein activity, and active Na^+ transport. **Saika** only teaches an effect based on the presence of basal lamina under new epithelia, whereas **Nowak** only teaches stimulation of

cell migration/spreading and decreasing cell death by ascorbic acid. Consequently, **Fahim, Rath, Saika** and **Nowak** do not teach or suggest all the claim limitations, and the combined references do not disclose anything related to recovery of mitochondrial function, Na^+-K^+-ATPase protein expression, Na^+-K^+-ATPase protein activity, and active Na^+ transport as claimed herein.

One of ordinary skill in the art would readily recognize that the cellular functions disclosed in **Fahim, Rath, Saika** and **Nowak** are different and distinct from those claimed in the present invention, and these different cellular functions may very well involve different cellular pathways. It is also well known in the art that a particular compound or agent may impact one cellular pathway but not the other. Therefore, absent any teaching or suggestion that the cellular functions/pathways disclosed in **Fahim, Rath, Saika** and **Nowak** and those claimed in the present invention share common features, one of ordinary skill in the art would not have the motivation and the requisite reasonable expectation of success to use ascorbic acid to recover mitochondrial function, Na^+-K^+-ATPase protein expression, Na^+-K^+-ATPase protein activity, and active Na^+ transport as claimed herein.

In view of the above remarks, Applicant submits that the combined teaching of **Fahim, Rath, Saika** and **Nowak** does not provide a person having ordinary skill in this art with the requisite expectation of successfully producing Applicant's claimed methods. The invention as a whole is not *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Accordingly, Applicant respectfully requests that the rejection of claims 1, 3-4, 11-13, and 15-16 under 35 U.S.C. §103(a) be withdrawn.

Respectfully submitted,

Date: Nov 6, 2003

Benjamin Aaron Adler, Ph. D., J.D.
Registration No. 35,423
Counsel for Applicants

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391
badler1@houston.rr.com

CLAIMS ON APPEAL

1. A method of recovering cellular functions *in vitro* in cells following injury, comprising the step of:

contacting said cells with ascorbic acid or a salt of ascorbic acid,

wherein said cellular functions are selected from the group consisting of proliferation, mitochondrial function, Na^+-K^+-ATPase protein activity, and active Na^+ transport.

3. The method of claim 1, wherein said ascorbic acid is L-ascorbic acid phosphate.

4. The method of claim 1, wherein the concentration of said ascorbic acid is from about 0.05 mM to about 0.5 mM.

11. A method of recovering cellular functions following injury in an individual in need of treatment, comprising the step of:

administering a therapeutically effective amount of ascorbic acid or a salt of ascorbic acid to said individual,

wherein said cellular functions are selected from the group consisting of proliferation, mitochondrial function, Na^+-K^+-ATPase protein expression, Na^+-K^+-ATPase protein activity, and active Na^+ transport.

12. The method of claim 11, wherein said injury is selected from the group consisting of halogenated hydrocarbons-induced nephrotoxicity, ischemia-induced acute renal failure, drug-induced acute renal failure, glomerulonephritis, skin abrasions, cuts and burns.

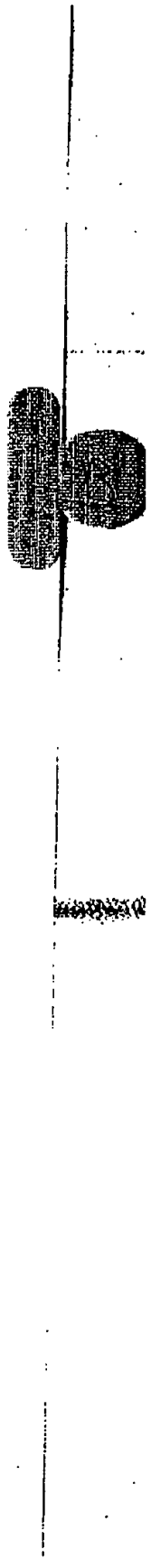
13. The method of claim 12, wherein said halogenated hydrocarbons is dichlorovinyl-L-cysteine.

15. A method of recovering cellular functions in an eye disease or following an injury to the eye of an individual in need of treatment, comprising the step of:

administering an ophthalmic composition comprising a therapeutically effective amount of ascorbic acid or a salt of ascorbic acid in an ophthalmically acceptable carrier to said individual,

wherein said cellular functions are selected from the group consisting of proliferation, mitochondrial function, Na^+-K^+-ATPase protein expression, Na^+-K^+-ATPase protein activity, and active Na^+ transport and wherein said ascorbic acid is in the concentration range of from about 0.05 mM to about 0.5 mM.

16. The method of claim 15, wherein said injury is selected from the group consisting of acute injury to the eye, eye injury associated with the over production of collagen in conjunctivitis or diabetes mellitus, and eye injury associated with the under production of collagen in rheumatoid arthritis.



of oxidative protein modification in relation to ischemia/reperfusion injury and)

L164 ANSWER 28 OF 68 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:439289 CAPLUS
DOCUMENT NUMBER: 127:131510
TITLE: Renal cell regeneration following oxidant exposure: inhibition by TGF-.beta.1 and stimulation by ascorbic acid
AUTHOR(S): Nowak, Grazyna; Schnellmann, Rick G.
CORPORATE SOURCE: Department of Pharmacology and Toxicology, University of Arkansas for Medical Sciences, Little Rock, AR, 72205-7199, USA
SOURCE: Toxicol. Appl. Pharmacol. (1997), 145(1), 175-183
CODEN: TXAPA9; ISSN: 0041-008X
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Renal proximal tubular cell (RPTC) monolayers exposed to the model oxidant tert-butylhydroperoxide (TBHP; 0.8 mM) for 1.5 h were 33 and 31% confluent after 1 and 4 days, resp. Control monolayers remained 100% confluent throughout the expt. Exogenous TGF-.beta.1 promoted monolayer deterioration by potentiating cellular death and suppressed EGF-stimulated regeneration of the RPTC monolayer. Net TGF-.beta.1 prodn. in injured RPTC increased 1.7- and 3.2-fold on Days 1 and 2, resp., and returned to control levels 4 days following TBHP treatment. An anti-TGF-.beta. antibody increased monolayer confluence to 50% and DNA content 1.3-fold 4 days after TBHP exposure. L-Ascorbic acid 2-phosphate (AscP) present only during the recovery period increased monolayer confluence to 67% but had no effect on RPTC proliferation, suggesting that AscP promoted monolayer regeneration by cellular migration/spreading. AscP present continuously had no effect on the extent of TBHP-induced injury but promoted regeneration of RPTC with increased monolayer confluence (1.8-fold) and DNA content (1.8-fold) and decreased cellular lysis by 52% 4 days following TBHP exposure. The results demonstrate that TBHP-induced injury increases net TGF-.beta.1 prodn. in RPTC and that autocrine TGF-.beta.1 inhibits regeneration of the monolayer by potentiating cellular injury and monolayer deterioration. The data also show that AscP is not cytoprotective during TBHP exposure but promotes RPTC regeneration by stimulating proliferation and migration/spreading and decreasing cellular death during the recovery period.
IT 50-81-7, Ascorbic acid, biological studies 23313-12-4,

Searched by Barb O'Bryen STIC 308-4291

L-Ascorbic acid 2-phosphate
RL: **BAC (Biological activity or effector, except adverse)**; BIOL (Biological study)
(TGF-.beta.1 and ascorbic acid effect on renal cell regeneration following oxidant exposure)

L164 ANSWER 29 OF 68 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:494349 CAPLUS
DOCUMENT NUMBER: 125:150779
TITLE: Anti-irritant skin formulations containing aluminum or tin cations
INVENTOR(S): Hahn, Gary Scott; Thueson, David Orel
PATENT ASSIGNEE(S): Cosmederm Technologies, USA
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO. KIND DATE APPLICATION NO. DATE

CORPORATE SOURCE: Central Research Laboratories, Santen Pharmaceutical Co., Ltd., Osaka, Japan.
SOURCE: JOURNAL OF OCULAR PHARMACOLOGY, (1994 Fall) 10 (3) 537-42.
Journal code: IRG; 8511297. ISSN: 8756-3320.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199502
ENTRY DATE: Entered STN: 19950314
Last Updated on STN: 19950314
Entered Medline: 19950227

AB In developing chick embryos, hydrocortisone induces cataract formation following a decrease in lens glutathione content but an increase in lipid peroxide content in lens, blood and liver. The preventive effects of ascorbic acid 2-O-alpha-glucoside (AA-2G) on these parameters were compared on cataract formation with those of ascorbic acid (AsA) and ascorbic acid 2-O-phosphate (AA-2P). In these tissues, AA-2G inhibited a decrease in glutathione content and an increase in lipid peroxide content more effectively than either AsA or AA-2P. Various tissues including lens and liver have alpha-glucosidase activity, strongly suggesting that AsA is enzymatically liberated from AA-2G in these tissues. In summary, these results suggest that AA-2G exerts a potent anti-cataract activity via a reduction in oxidative damage through AsA release.

L164 ANSWER 2 OF 68 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 93252299 MEDLINE
DOCUMENT NUMBER: 93252299 PubMed ID: 8486304
TITLE: Ascorbic acid phosphate ester and wound healing in rabbit corneal alkali burns: epithelial basement membrane and stroma.
AUTHOR: Saika S; Uenoyama K; Hiroi K; Tanioka H; Takase K; Hikita M
CORPORATE SOURCE: Department of Ophthalmology, Wakayama Medical College, Japan.
SOURCE: GRAEFES ARCHIVE FOR CLINICAL AND EXPERIMENTAL OPHTHALMOLOGY, (1993 Apr) 231 (4) 221-7.
Journal code: FPR; 8205248. ISSN: 0721-832X.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930618
Last Updated on STN: 19930618
Entered Medline: 19930607

AB We examined the effect of L-ascorbic acid 2-phosphate (P-Asc) on the healing of alkali-burned corneas in rabbits. Round filter paper containing 1 N NaOH was applied to the central cornea for 60 or 120 s to produce the alkali burn. Animals were treated with topical saline, 10% ascorbate, or 6.5% P-Asc applied on the cornea. The corneas were then examined histologically. Burned stroma showed no toluidine blue staining, indicating a loss of glycosaminoglycan. In the 60-s burn group, P-Asc reduced the size of the unstained area as compared with the control. Transmission electron microscopy showed basal lamina under new epithelia in the corneas treated with ascorbate or P-Asc, but not in controls. These observations support the theory that P-Asc may have a therapeutic role in the repair of corneal alkali burns.

L64 ANSWER 3 OF 68 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 93217344 MEDLINE
DOCUMENT NUMBER: 93217344 PubMed ID: 8463733
TITLE: Effect of ascorbic acid 2-O-alpha-glucoside on